Spontaneous Remission of Retroperitoneal Fibrosis in a Patient with Inherited Thrombophilia

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Retroperitoneal fibrosis (RPF) is a rare condition characterized by a diffuse or localized fibroblastic proliferation associated with chronic inflammation. RPF is generally idiopathic, but can also be secondary to the use of certain drugs, malignant diseases, infections, and surgery. Treatment of RPF aims to relieve ureteral obstruction and to induce disease regression, and includes the use of steroids combined or not with other immunosuppressive agents. We present the case of a 35-years old female with a medical history of transient ischemic stroke, myocardial infarction, miscarriage and inherited thrombophilia, who was diagnosed in our Department with idiopathic RPF. Due to the mentioned associated comorbidities, no immuno-active treatment could be initiated. After one year, MRI exam showed significant spontaneous decrease of RPF mass. Although an uncommon event, the spontaneous resolution of idiopathic RPF could encourage in some selected cases a conservative management. By our knowledge, no previously cases of spontaneously remitted RPF in patients with inherited thrombophilia have been reported.

Keywords: retroperitoneal fibrosis, inherited thrombophilia, spontaneous remission

Retroperitoneal fibrosis (RPF), also known as Ormond's disease, is a rare condition characterized by a diffuse or localized fibroblastic proliferation associated with chronic inflammation [1-5]. Despite scientific advances, there is no standard definition that clearly defines the criteria that must be accomplished for the diagnosis of RPF [2]. RPF is generally idiopathic, but can also be secondary to the use of certain drugs, malignant diseases, infections, and surgery [1]. Although benign, the compression or obstruction of the ureters and vascular structures can be an important health hazard [1]. Treatment of RPF aims to relieve ureteral obstruction and to induce disease regression, and includes the use of steroids combined or not with other immunosuppressive agents [6]. Although an uncommon event, the spontaneous resolution of RPF could encourage in some selected cases a conservative management.

Experimental part

A 35 years old female was referred to our Department for right ureterohydronephrosis observed during the ultrasound exam. She initially presented to her general practitioner with right renal colic 1 week before admission in the hospital. The patient had a medical history of transient ischemic stroke, myocardial infarction, miscarriage and inherited thrombophilia MTHFR C677T positive (methylene tetrahydrofolate reductase C677T genotype). She denied smoking and also any exposure to dust, including asbestos. Her chronic medication included only clopidogrel 75 mg o.d.

On admission, the physical examination did not reveal any eruptions or swelling of joints or superficial lymph nodes; blood pressure and pulse rate were also normal. The abdominal ultrasonography did not show other abnormalities except right ureterohydronephrosis. The laboratory findings revealed: white blood count 7890/μL, serum creatinine 0.58 mg/dL, erythrocyte sedimentation rate (ESR) of 12 mm/h, C-reactive protein (CRP) of 0.52 mg/dL; the other routine blood tests were within normal limits. Urine exam showed no abnormalities, and urine culture was sterile.

An enhanced computed tomography (CT) scan was performed (fig. 1). It revealed a retroperitoneal tissue mass encasing the aorta, inferior vena cava and the lower lumbar and iliac segments of the right ureter with secondary ureterohydronephrosis; a RPF was suspected. No other abnormalities regarding the kidneys or the intra-abdominal solid organs were found, and also no lymphadenopathy was revealed. For the protection of the right kidney a double J stent was inserted under fluoroscopic guidance.

The patient underwent several blood and imaging tests in order to find a possible cause of retroperitoneal fibrosis. Total anti-nuclear antibodies were 8.60 UA/mL (normal range 0-20 UA/mL) according to ELISA testing, anti-phospholipid IgG antibodies 1.26 U/mL (normal range <12

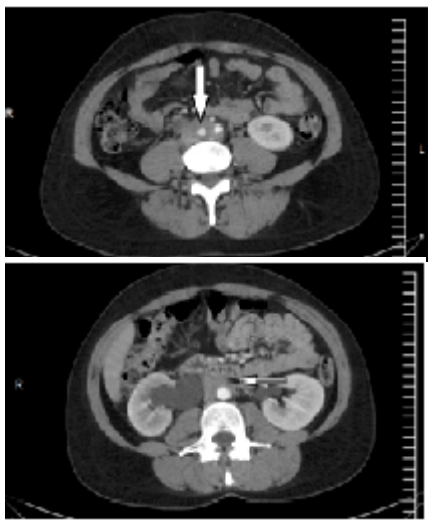

Fig. 1. CT-scan showing retroperitoneal mass and right ureterohydronephrosis

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U/mL) and anti-phospholipid IgM antibodies 0.20 U/mL (normal range <12 U/mL). Testing for thyroid function, rheumatoid factor, p-ANCA and c-ANCA, proteinuria or tumor markers (cancer antigen 19-9, alpha-fetoprotein, carcinoembryonic antigen) were all negative. Serum protein electrophoresis showed no abnormalities, and also serum levels of Ig G, Ig M, and Ig E were all within normal range. The pulmonary radiograph and the upper endoscopy were performed without notable pathologic findings. Therefore, the diagnosis of idiopathic RPF was considered.

After discussing therapeutic options, the patient declined immunosuppressive therapy with corticosteroids due to possible side effects taking into account her medical history. The double J stent was replaced after 3 months. One month following the replacement the patient was evaluated for bothersome lower urinary tract symptoms. The abdominal X-ray showed a dislodged ureteral stent but no hydronephrosis at the sonographic evaluation. In this situation the double J stent was removed. The magnetic resonance imaging (MRI) performed one year later revealed a decrease of the retroperitoneal fibrotic mass by 85% compared to the initial CT scan and no hydronephrosis was present (fig. 2).

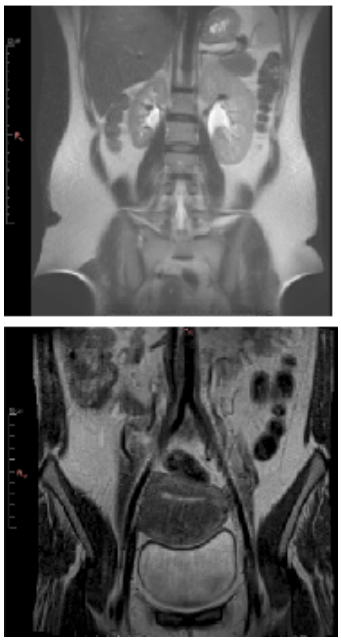

Fig. 2. MRI one year after double J stent removal

Results and discussions

RPF can be of 2 types: idiopathic and secondary. While incidence of secondary forms of RPF is unknown, literature data shows that idiopathic RPF is quite a rare disease, with an incidence between 0.1-1.3 cases/100,000 persons-years [7,8], and a prevalence of 1.4 cases/100,000 inhabitants [8]. According to *Kasales et al.* it presents commonly after the fourth decade of life and has a male preponderance [9].

The pathogenesis of retroperitoneal fibrosis is still unclear and probably multifactorial. Idiopathic RPF is considered actually to be a part of chronic periaortitis, a disease characterized by inflammatory fibrosis surrounding aorta and other large arteries [1,10]. Several authors suggested that chronic periaortitis could be a consequence of a local inflammatory reaction to oxidized low-density lipoproteins (LDL) and ceroid (a lipoproteic polymer that results from LDL oxidation within plaque macrophages), which are often found in the atherosclerotic plaques of the abdominal aorta [11-13]. Genetics could also play a role in the etiology and pathogenesis of idiopathic RPF. In a case-control study of 38 patients, *Martorana et al.* indicate that the disease is significantly associated with HLA-DRB1*03; this is an allele linked to various autoimmune diseases (e.g. type 1 diabetes mellitus, myasthenia gravis or systemic lupus erythematosus) in patients associating or not renal impairment [14-17]; authors found it in 48.5% of the patients with periaortitis and in only 16% of controls [18]. Recently, the immune system involvement in the pathogenesis of chronic periaortitis and RPF was revealed and many authors urged to rethink RPF as an IgG4-related disease [19-22]. Unfortunately, not many reports have been published on IgG4-related retroperitoneal fibrosis. Most of studies which led to widespread recognition of retroperitoneal fibrosis as a condition caused by IgG4-related disease, derived from researches on autoimmune pancreatitis (AIP). *Hamano et al.* found in both pancreatic and retroperitoneal lesions from patients with AIP an abundant infiltration of IgG4-positive plasma cells [22]. Based on this findings, *Kamisawa et al.* proposed a new clinic-pathological entity (IgG4-related sclerosing disease), and suggested that AIP is a pancreatic lesion reflecting this systemic disease [23]. According to *Vaglio et al.* high IgG4 levels have been linked to IgG4-related RPF, but a systematic assessment of IgG4 in idiopathic RPF is lacking [24]. Therefore, the exact proportion of patients with high serum IgG4, as well as the prognostic significance of this biomarker are still unknown.

Secondary retroperitoneal fibrosis is caused by a broad range of factors (table 1). Most common encountered cause is use of particular drugs, which mainly include derivatives of ergot alkaloids (methysergide) and dopamine agonists; beta blockers, hydralazine, and analgesics (e.g. aspirin, phenacetin) are also associated with retroperitoneal fibrosis, but their causative role is controversial [1,25,26]. We found in our patient only chronic use of

Causes	Examples
Malignancies	Carcinoid, Hodgkin's and non-Hodgkin's lymphomas, sarcomas, carcinomas of the colon, prostate, breast, stomach
Infections	Blastomyces, tuberculosis, histoplasmosis, actinomycosis
Drugs	Methysergide, ergotamine, beta-blockers, pergolide, bromocriptine, methyldopa, hydralazine, analgesics
Surgery	Lymphadenectomy, colectomy, hysterectomy, aortic aneurysmectomy
Radiotherapy	Testicular seminoma, colon carcinoma, pancreatic carcinoma
Others	Histiocytoses, Erdheim-Chester disease, amyloidosis, trauma, barium enema, asbestos

Table 1
MAJOR CAUSES OF SECONDARY RETROPERITONEAL FIBROSIS

**according to Vaglio et al. [1]*

clopidogrel, an antiplatelet drug not considered to be involved in the etiology of RPF. Smoking and exposure to asbestos are also considered risk factors for idiopathic RPF [7,8,27]; in our patient, no such associations were encountered.

RPF does not have a specific symptom, usually systemic symptoms (e.g., fatigue, anorexia, weight loss) coexist with lumbar, flank or abdominal pain [10,28]. Pain is frequently dull and does not modify with position, in some cases it transiently responds to nonsteroidal anti-inflammatory drugs [2]; it may mimic a ureteral colic if the ureter is involved [29,30], as it happened in our patient. Frequency, hematuria, and dysuria are less encountered manifestations [24].

There are no specifically laboratory findings associated with retroperitoneal fibrosis; however, an increased white blood cell count, erythrocyte sedimentation rate or C-reactive protein levels can be seen as a reflection of acute inflammation [7]. According to Scheel et al. significant normochromic normocytic anemia may occurs in 25 to 50% or patients at the time of presentation, and 50 to 100% of patients will have an elevated erythrocyte sedimentation rate or C-reactive protein [31]. In our patient all were in normal range. In addition, according to the same authors, 25 to 60% of patients with RPF will be positive for antinuclear antibodies [31]. In our patient antiphospholipid antibodies and antinuclear antibodies were in normal range. As presented in table 1, several other conditions have been linked to secondary RPF [1]; in our patient, we could not identify neither infectious nor malignant diseases. By our knowledge, no author linked inherited thrombophilia to RPF.

Although the starting point of fibrosis is the periaortic tissue, ureteral involvement is the most common disease-related complication [24]. Ureteral obstruction can be unilateral or bilateral, and in the latter case chronic kidney disease is frequent; in cases with unilateral ureterohydronephrosis, contralateral obstruction can occur weeks to years after the initial presentation [32,33]. Imaging techniques, are very useful to diagnose retroperitoneal fibrosis. As in our case, because it is a simple and minimally invasive technique, the ultrasound is usually performed first. The major drawback is the very low sensitivity, and is rather important in determining the presence or absence of hydronephrosis. CT scan and MRI are more useful. According to Vivas et al., on CT images, retroperitoneal fibrosis is depicted as a soft tissue mass encasing the aorta, which often spreads laterally to involve the inferior vena cava and urinary duct and up to 15% of patients have additional fibrotic processes outside the retroperitoneum [34]. On MRI images, retroperitoneal fibrosis shows low signal intensity on T1-weighted images, and high signal intensity on T2-weighted images. Ozaki et al. used fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) for assessment of the presence/absence of retroperitoneal fibrosis as well as other lesions of IgG4-related disease [35]; the authors concluded that FDG-PET is a useful tool for differentiating autoimmune pancreatitis from suspected pancreatic cancer, if the accumulation pattern and extra-pancreatic involvement are considered.

There is currently little evidence regarding the best management of these patients as no controlled drug-related trials have been undertaken. Before stating the treatment, if there is ureteric obstruction, for the protection of the renal unit, ureteric stenting is often required [24]. After the stents are in place the medial deviation of the ureters can be seen on abdominal X-Ray as the stent can be visualized in the lines of the ureters. If in the past surgical ureterolysis with intraperitonealization and omental wrapping of the ureters was the first-line approach, in our days conservative procedures (e.g., double-J stent or nephrostomy placement) followed by medical therapy are preferred [24,31]. According to Vaglio et al. first-line therapy is represented by glucocorticoids with initial doses of 0.75-1 mg/kg per day of prednisone gradually tapered to 5–7.5 mg o.d. within 6-9 months [24]. The same authors stated that remission rates after steroid therapy range between 75 and 95% and mean mass thickness reduction is around 50%. In patients with RPF associated with immunoglobulin G4-related disease, according to Fujimori et al. the response to steroid therapy is generally good [36]; however, some patients are resistant to steroid, although the mechanism of steroid resistance is unclear. In cases of treatment failure and persistent chronic residual hydronephrosis, surgical ureterolysis may be required. Glucocorticoids therapy is associated with various systemic manifestations among which hypercoagulability is also listed [37]. In addition, Souverein et al. noticed in a very large cohort of patients a significant association between chronic glucocorticoid use and increased risk of heart failure and a smaller increased risk of ischemic heart disease but not ischemic stroke or transient ischemic attack [38]. In our patient the risks of glucocorticoids side-effects would have been substantial considering her inherited thrombophilia and history of ischemic stroke. An alternative to glucocorticoids proposed in patients experiencing steroid-related toxicity or when there are contraindications to glucocorticoids use is tamoxifen, an anti-estrogen agent with potential antifibrotic activity [39]. However, Vaglio et al. in a randomized controlled trial, showed that an 8 month treatment with tamoxifen was significantly less effective than a treatment with prednisone of equal duration in maintaining remission in patients treated with prednisone induction [33]. The same authors recall anecdotal reports demonstrated the efficacy of biologic agents, namely the anti-IL6 receptor tocilizumab, and rituximab, a B cell-depleting agent also effective in IgG4-related diseases [40,41].

The natural evolution of untreated RPF is not well known, because most patients receive surgical and/or medical intervention, but we assume that bilateral hydronephrosis will lead to end-stage renal disease secondary to obstructive nephropathy [42-44]. Spontaneous remission of RPF is very uncommon but not impossible. One of the first authors to report a case of spontaneous remission of RPF was Robbe et al. in 1983, which reported the case of a 79-year-old man with right ureterohydronephrosis at the CT scan secondary to a soft tissue density mass adjacent to the dilated right common iliac artery [45]. They performed a nephrostomy and after only a week a nephrostogram revealed some distortion at the level of the common iliac artery but no obstruction to contrast medium passing from the right kidney to the bladder. In this situation the authors considered a spontaneous remission of the fibrotic tissue and the nephrostomy drain was removed. Templ et al. reported the case of a 64-year-old man with sigma cancer in which the CT scan showed revealed a significant reduction of the retroperitoneal masses after hemicolectomy and before induction of chemotherapy [46]. Khezri et al. also reported the spontaneous remission of the RPF in a 70-year-old white man with adenocarcinoma of the prostate with ureterohydronephrosis treated with leuprolide; apparently, CT-guided needle aspiration biopsy of the retroperitoneal mass did not revealed malignant cells [47]. The CT scan of the abdomen performed 1 month after a ureteral stent placement, showed marked resolution of previous findings [47]. Williams et al. reported the case of a 54-year-old woman with no malignancy but with

hydronephrosis secondary to RPF who declined the use of corticosteroid treatment due to concerns for the potential side effects; the para-aortic fibrotic mass decreased in size over a 12-month period, the maximal thickness of the cuff tissue anterior to the aorta had reduced in size from 13.32 mm to 5.88 mm [48]. One of the two cases, by our knowledge, of IgG4 related RPF with spontaneous remission was reported by Yamakawa et al.; the authors performed a CT-guided biopsy of the retroperitoneal mass surrounding the aorta which showed lymphoplasmocytic infiltration and fibrosis, and the infiltration of IgG4+ plasma cells with a ratio of IgG4+/IgG+ cells >50% [49]. After 2 months, CT scan showed an improvement of the retroperitoneal lesions, and also a decrease of IgG4 levels from 185 mg/dL to 41 mg/dL [49]. The other one was reported by Miura and Miyachi in a 80-year-old Japanese man with IgG4-related retroperitoneal fibrosis and sclerosing cholangitis independent of autoimmune pancreatitis; nevertheless, in this case, after a 5-year history of spontaneous clinical remission, there was an elevation of serum IgG4 levels and recurrence of renal dysfunction owing to bilateral hydronephrosis caused by a reemergence of the retroperitoneal mass [50]. Subsequent to this relapse, oral prednisolone therapy was introduced [50].

All cases reported with spontaneous remission of RPF were over 50 years old, and none had inherited thrombophilia.

Conclusions

RPF is still a mysterious fibro-inflammatory disease with an unclear etiology which can affect retroperitoneal structures like aorta, inferior vena cava or the ureters. Although in most patients, immunosuppressive therapy is the first line treatment, in some particular cases when there are serious concerns regarding the potential for side effects, monitoring the ongoing disease evolution rather than proceeding to corticosteroid treatment can be justified. By our knowledge, no previously cases of spontaneously remitted RPF in patients with inherited thrombophilia have been reported.

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